REMARKS

Claims 51-76, 79-92, 95 and 97 are pending in this application. Claims 51-76, 79-92, 95 and 97 have been rejected. Claims 82 and 83 have been canceled. Claims 63, 73, and 74, have been amended. Claim 73-74 have been amended as supported on page 14, lines 10-11 and throughout the specification. Claim 63 has been amended to correct typographical errors and to clarify the invention, as supported throughout the specification. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Double Patenting Rejection

A. Doctrine of Obviousness-type Double Patenting

Claims 51-76, 79-92, 95 and 97 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,355,791 and allowed Application No. 09/848,385 in view of Peters (Anal. Chem. 1997, 69, 3646-3649) Huang (J. of Chromatography 788 (1997) 155-164), and Tomer (Mass Spectrometry Reviews 1994, 13, 431-457). The Examiner suggests that at best

the claims differ from U.S. Patent No. 6,355,791 and allowed application No. 09/848,385 in reciting the use of a fused silica capillary, the clarity of covalent bonding and a size of less than one millimeter in diameter. Peters (Anal. Chem. 1997, 69, 3646-3649)(page 3646 the Abstract and page 3649, column 2) is suggested to teach use of a fused silica column eliminates the need for initial chemical modification of the walls of the capillary. Huang (J. Of Chromatography 788 (1997) 155-164) is suggested to teach that covalently bound vinyl groups offer anchoring sites for the polymer. Tomer (Mass Spectrometry Reviews, 1994, 13, 431-457) is suggested to teach that smaller diameter columns is the trend in chromatography because of improved concentration detection limits and the small amounts of sample available for analysis. The Examiner suggests that it would have been obvious to use a fused silica column in each of U.S. Patent No. 6,355,791 and allowed Application No. 09/848,385 because Peters discloses that use of a fused silica column eliminates the need for initial chemical modification of the walls of the capillary. It is further suggested that it would have been obvious that the polymer is covalently bound because Huang (J. Of Chromatography 788 (1997) 155-164) discloses that covalently bound vinyl groups offer anchoring sires for the

polymer, and that it would have been obvious to use a column less than 1 millimeter in diameter because Tomer discloses that smaller diameter columns is the trend in chromatography because of improved concentration detection limits and the small amounts of sample available for analysis.

Applicants respectfully disagree. However, in an earnest attempt to facilitate prosecution in this case, Applicants are herewith submitting a terminal disclaimer in compliance with 37 CFR 3.73(b). Submission of this terminal disclaimer with respect to U.S. Patent 6,355,791 and Application 09/848,385 (now U.S. Patent No. 6,521,123) both assigned to Transgenomic, Inc. is believed to render this rejection moot.

Therefore, withdrawal of this rejection is respectfully requested.

B. Claim 74 Rejection under 35 U.S.C. 101

Claim 74 is further rejected under 35 U.S.C. 101 as double patenting claim 73 because claim 74 has the same scope as 73. Claim 74 has been amended as supported throughout the specification to recite a tube having an inner diameter in the range of 10 micrometer to 500 micrometer. Support for this

amendment is provided throughout the specification and at page 14, lines 10-11.

Withdrawal of this rejection is respectfully requested.

II. Rejection under 35 U.S.C. 112, second paragraph

Claim 74 is rejected under 35 U.S.C. 112 second paragraph as being an improper dependent claim because it is suggested that it does not further limit claim 73.

In an earnest effort to advance prosecution of this case as set forth above, Applicants have amended claim 74 to further limit claim 73, and recite that the inner diameter of the tube is in the range of 10 micrometers to 500 micrometers.

Support for this amendment is provided throughout the specification and at page 14, lines 10-11.

Withdrawal of this rejection is respectfully requested.

III. Rejection under 35 U.S.C. 102(a)/103(a)

A. Gusev as Primary Reference

Claims 51-76, 79-92, 95 and 97 are rejected under 35 U.S.C. 102(a) as anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over Gusev, J. Of Chromatography 1999, pages

273-290. The claims are suggested to read on Gusev, J. Of Chromatography 1999 pages 273-290. It is suggested that it would have been obvious to optimize the elements of Gusev to enhance separation.

Claims 57-58 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gusev in view of Peters (U.S. Patent No. 5,929,214). The Examiner suggests that at best, the claims of Gusev differ in reciting channels sufficiently large to allow convective flow. Peters discloses that large channels which allow convective flow also allow high flow rates through a monolith. It suggested that it would have been obvious to have sufficiently large channels to allow convective flow in Gusev because Peters discloses that large channels that allow convective flow also allow high flow rates through a monolith.

Claim 91 is rejected under 35 USC 103(a) as being unpatentable over Gusev in view of Girot (US Patent 6,045,697). At best the claim differs from Gusev in reciting use of a tetrahydrofuran porogen. Girot discloses that tetrahydrofuran is a suitable porogen. It is suggested to have been obvious to use tetrahydrofuran as a porogen because Girot discloses that tetrahydrofuran is a suitable porogen.

Claim 95 is rejected under 35 USC 103(a) as being unpatentable over Gusev, in view of either Huber or Griffey. It is suggested that the claim differs from Gusev in reciting use of a mass spectrometer. Huber discloses electrospray mass spectrometry allows accurate molecular determinations in the picomole range. Griffey discloses that electrospray mass spectrometry is a gentle sensitive method of analysis. It would have been obvious to use mass spectrometry in Gusev either because Huber discloses electrospray mass spectrometry allows accurate molecular determinations in the picomole range or because Griffey discloses that electrospray mass spectrometry is a gentle sensitive method of analysis.

Applicants respectfully disagree.

Under 35 U.S.C. 102(a) a person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

First, Gusev does not describe the present invention. Gusev teaches the *in situ* preparation of a porous styrenic monolithic packing inside capillary to separate standard proteins by reverse phase micro-HPLC with gradient elution. Gusev does not teach the

use of channels sufficiently large to allow convective flow. Furthermore with regard to claim 91, Gusev recites the use of a tetrahydrofuran porogen. Further still Gusev does not recite the use of a mass spectrometer.

Second, Gusev is not a proper prior art reference, as the present invention was invented prior to the publication of Gusev. Accordingly, in an earnest attempt to facilitate prosecution in this case, Applicant is herewith submitting an Affidavit of Prior Invention under 37 CFR 1.131. This affidavit shows invention of the subject matter claimed prior to the effective date of the Gusev reference, September 3, 1999. Applicants were diligently reducing their invention to practice via laboratory testing and confirmation, as early as August 1998. The present invention realized the first synthesis of PS/DVB monolith using porogens on August 6, 1998. The first successful separation of oligonucleotides on a PS/DVB monolith was February 9, 1999. Therefore, submission of this affidavit is believed to invalidate Gusev as a prior art reference and render this rejection under 35 U.S.C. 102(a)/103(a) moot. The remaining secondary references,

namely, Peters, Huber, Griffey or Girot cannot be held to teach or suggest all of the claim limitations of the present invention.

Reconsideration and withdrawal of this rejection is respectfully requested.

B. Frechet or Hatch as Primary Reference

Claims 51-66, 71, 73-76, 79-85 and 95 are rejected under 35 USC 103(a) as being unpatentable over either Frechet or Hatch in view of Peters, Huang and Tomer. It is suggested that the claims differ from each of Frechet and Hatch in reciting use of a fused silica capillary, the clarity of covalent bonding, and a size of less than one millimeter in diameter. Frechet is suggested to disclose a glass column. Peters is suggested to disclose that the use of a fused silica column eliminates the need for initial chemical modification of the walls of the capillary. Huang is suggested to teach that covalently bound vinyl groups offer anchoring sites for the polymer. It is suggested that it would have been obvious to use a fused silica column in either Frechet or Hatch because Peters discloses that use of a fused silica column eliminates the need for initial chemical modification of the walls of the capillary. Further, it is suggested to make

obvious that the polymer is covalently bound because Huang discloses that covalently bound vinyl groups offer anchoring sites for the polymer.

Claims 86-92 and 97 are rejected under 35 U.S.C. 103 (a) as being unpatentable over either Frechet or Hatch in view of Peters and Tomer. The Examiner suggests that Tomer discloses that smaller diameter columns is the trend in chromatography because of improved concentration detection limits and the small amounts of sample available for analysis. It is suggested that it would have been obvious to use a column less than 1 millimeter in diameter because Tomer discloses that smaller diameter columns is the trend in chromatography because of improved concentration detection limits and the small amounts of sample available for analysis.

Claims 57-58 are rejected under 35 USC as being unpatentable over either Frechet or Hatch in view of Peters, Huang in view of Peters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Peters. Peters is suggested to disclose that large channels that allow convective flow also allow high flow rates through a monolith. It would have been obvious to have sufficiently large channels to allow convective flow in either Frechet or Hatch in view of Peters,

Huang and Tomer, because Peters discloses that large channels that allow convective flow also allow high flow rates through a monolith.

Claim 91 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Peters and Tomer as applied to claims 86-92 and 97 above and further in view of Girot. The claims are suggested to differ from either Frechet or Hatch in view of Peters and Tomer in reciting a tetrahydrofuran is a suitable porogen. It is suggested to be obvious to use tetrahydrofuran as a porogen in either Frechet or Hatch in view of Peters because Girot discloses that tetrahydrofuran is a suitable porogen.

Claim 95 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Paters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Huber or Griffey. The Examiner suggests that the claims differ in reciting the use of a mass spectrometer. Huber is suggested to disclose electrospray mass spectrometry allows accurate molecular determinations in the picomole range. Griffey is suggested to disclose that electrospray mass spectrometry is a gentle sensitive method of analysis. It is suggested to be obvious to use mass spectrometry

in either Frechet or Hatch in view of Peters, Huang and Tomer, either because Huber discloses electrospray mass spectrometry allows accurate molecular determinations in the picomole range or because Griffey discloses that electrospray mass spectrometry is a gentle sensitive method of analysis.

Applicants respectfully traverse.

The present invention is a device for separating a mixture of polynucleotides. The device comprises a polymeric monolith having non-polar chromatographic surfaces, with an underivatized poly(styrene-divinylbenzene) matrix. The monolith is contained within a fused silica tube, and is immobilized by covalent attachment at the innerwall of said tube. The monolith has a high separation efficiency. As recited on page 17, line 30 of the specification, the instant invention is based on the surprising and unexpected discovery that an underivatized poly(styrene-divinylbenzene) monolith exhibits highly efficient DNA separation performance. This finding was highly unexpected, as evidenced by published patent application WO 00/15778 which teaches that underivatized poly(polystyrene/divinylbenzene) structures are not desirable for DNA separations. None of the prior art recited in the present office action by the Examiner teaches the use of

underivatized poly(polystyrene/divinylbenzene) structures for DNA separations.

Frechet teaches a continuous liquid chromatographic column containing a separation medium in the form of macroporous polymer plug which stretches across the internal cross sectional area of the tube so that the sample must pass through the plug. The plug contains small and large pore. The column is not specifically taught as useful for DNA separation, but rather as an alternative separation means for any separation which can be done with a packed column. Frechet does not teach or suggest a monolith in a fused silica.

At the onset it is respectfully pointed out that Hatch was filed on September 16, 1998. This foiling is after the present invention was discovered as demonstrated by the attached Affidavit of Prior Invention under 37 CFR 1.131. Therefore Hatch cannot be considered to be a valid prior art reference. Hatch teaches a monolithic polymer matrices for separation by liquid chromatography. Some embodiments of the matrices may be used for separation of bio-organic molecules. The matrix is formed from polymerization of a monomer or a combination of monomers selected fro C3 to C30 alkyl methacrylates.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The present invention cannot be considered obvious by the recited references either taken either alone or combined. There is no suggestion or motivation, in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. The present invention has an unexpected result. For example, underivatized poly(polystyrene/divinylbenzene) structures were not considered to be desirable for DNA separations, see discussion *supra*. Further, none of the prior art

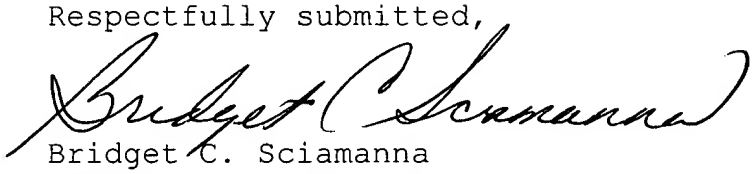
recited in the present office action by the Examiner teaches the use of underivatized poly(polystyrene/divinylbenzene) structures for DNA separations. Additionally, the recited art does not teach all of the claim limitations. Neither of the primary references, Frechet nor Hatch, disclose a polymeric monolith having non-polar chromatographic surface with an underivatized poly(styrene-divinylbenzene) matrix for DNA separation. Further neither primary reference teaches such a monolith is contained within a fused silica tube. The Examiner suggests that Peters, discloses the use of a fused silica column which eliminates the need for initial chemical modification of the walls of the capillary. While Peters recites in the abstract that a untreated fused silica capillary is used, Peters in no way teaches or suggests the use of underivatized poly(styrene-divinylbenzene) matrix contained within a fused silica tube, as required by the present invention. Similarly, neither Huang, Tomer, Huber nor Griffey disclose the use of an underivatized poly(styrene-divinylbenzene) matrix. Accordingly, none of the references, individually or combined, can be deemed to teach the limitations of the present invention.

Withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



Bridget C. Sciamanna
Registration No. 47,333

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515